Author's response to reviews

Title: Bevacizumab plus FOLFIRI or FOLFOX in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study.

Authors:

Astrid Lièvre (astrid.lievre@wanadoo.fr)
Emmanuelle Samalin (Emmanuelle.Samalin@valdorel.fnclcc.fr)
Emmanuel Mitry (emmanuel.mitry@apr.aphp.fr)
Eric Assenat (eric.assenat@valdorel.fnclcc.fr)
Christine Boyer-Gestin (Christine.Gestin-Boyer@valdorel.fnclcc.fr)
Céline Lepère (celine.lepere@apr.aphp.fr)
Jean-Baptiste Bachet (jbbachet@worldonline.fr)
Fabienne Portales (fabienne.portales@valdorel.fnclcc.fr)
Jean-Nicolas Vaillant (jncvaillant@yahoo.fr)
Marc Ychou (Marc.Ychou@valdorel.fnclcc.fr)
Philippe Rougier (philippe.rougier@apr.aphp.fr)

Version: 3 Date: 18 June 2009

Author's response to reviews: see over
Response to the reviewers

Manuscript MS: 1172410992367884
Title: Bevacizumab plus FOLFIRI or FOLFOX as third and further line treatment in metastatic colorectal cancer patients: a retrospective study.

Reviewer 1

1. What defined a line of therapy?
A line of chemotherapy was defined as the use of a chemotherapy regimen that is continued until tumor progression or unacceptable toxicity.

2. How was progression on first-line and second-line therapy defined?
Tumor progression on first or second-line chemotherapy was defined by CT scan according to the RECIST criteria. We modified the following sentence in the Patient characteristics section to specify this point: « all the patients... who had been previously treated with a fluoropyrimidine (e.g., fluorouracil or capecitabine) plus irinotecan and/or oxaliplatin with no response to treatment (as defined by tumor progression according to the RECIST criteria [11] or unacceptable toxicity) »

3. Was there central review of the first-line and second-line scans to verify progression?
There was no central review of CT-scans but all of them had been prospectively read in each center by a radiologist specialized in digestive oncology.

4. What is the breakdown of regimens that constitute a line of therapy for each patient?
a. This is especially important for patients who received more than two lines of therapy before entering the study.
We added in the Results – Patients characteristics section a sentence with the details of the regimens received by the patients who received more than 2 lines of chemotherapy before receiving bevacizumab:
« Among patients who were treated by bevacizumab in 4th line or further (n=20), cetuximab was used in the vast majority of them (n=19), five patients previously received a monotherapy of fluoropyrimidine (capecitabine ou 5FU), four patients were treated by the association of capecitabine and mitomycin-C and five by hepatic arterial infusion of oxaliplatin and intraveinous LV5FU2. »

5. Were patients previously treated with bevacizumab excluded?
Yes. This is mentioned in the Methods - Patients characteristics section (« ...patients who had not the opportunity to receive bevacizumab at an earlier line of chemotherapy »).

6. The title says the study was for patients treated in third line or further, yet there are data from a patient in the study who were treated second line, why is that?
As it is rightly underlined by the reviewer, a patient was actually treated in second-line by bevacizumab plus FOLFIRI. We included this patient because he was progressing under a first-line combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX regimen). This clarification was noted in the last sentence of the Results – Patients characteristics section:
« Bevacizumab was combined with FOLFIRI in 19 cases and with FOLFOX in 12 cases ... and one patient was treated in second line after a progression under a combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX regimen). »

7. How do the authors explain a disease control rate of 55% in the ‘later’ line group that is statistically significant when compared to the 25% disease control rate in the fourth line group. Without doing the statistical testing myself, I don't
see how with only 10 patients in each group, we can claim the additional three patients with disease control achieve a level of statistical significance, and I suspect there is great overlap of confidence intervals (moreover, the text states these numbers come from table 2, but not all the groups mentioned are listed in table 2).

We apologize for not being clear enough in our manuscript. In fact, as it can be found in the table 2, we pooled the response rate of the only patient treated in 2nd-line with those of the patients treated in 3rd-line by bevacizumab and compared them with the response rates of the patients treated in 4th-line and further (5/11=45.5% vs 5/20=25%). Same thing has been done for disease control rates.

We changed the following sentence and separated response rates and disease control rates in the Results – Response rates section to be clearer: « The response rate was 45.4% when bevacizumab was administered in 2nd and 3rd-line and 25% when it was administered in 4th line and more respectively (table 2; p=0.024).” and « The disease control rate was 100% when bevacizumab was administered in 2nd and 3rd line and 55% when it was administered in 4th line and more respectively (table 2; p=0.008).”

However, we agree with the reviewer that the number of patients in each group is very low, which makes that our data have to be taken with caution as we stated in the Discussion section (see below).

8. How do the authors explain the results in comparison to the outcome data for secondline FOLFOX4 from E3200 (Giantonio, et al) in which overall response for the bevacizumab + FOLFOX was 22%, OS was 12.9 months, and PFS was 7.2 months—all numbers considerably less yet from a much larger study in less pretreated patients.

Our results are certainly explained by the low number of patients included in our study. Furthermore, patients who received bevacizumab during the period of the study were probably highly selected by the physicians in view of the fact that bevacizumab was not registered in this setting but only in first line treatment of metastatic colorectal cancer. Finally, this is a retrospective study which is necessarily associated with biases.

We added a sentence in the Discussion section to underline the limits of our study: « These response and survival rates are much higher than those reported by Giantonio et al. with the combination of FOLFOX plus bevacizumab in second line treatment in patients previously treated by fluoropyrimidine and irinotecan, which might be certainly explained by the small size and the retrospective nature of our study. Furthermore, patients who received bevacizumab during the period of the study were highly selected because bevacizumab was not registered in this setting but only in first line treatment. For these reasons, our results have to be taken with caution. However, they are nonetheless interesting in third-line treatment where few molecules have been shown to be effective. »

9. There should be overall toxicity data.

We added chemotherapy-induced toxicity, which are summarized in a additional table (Table 3) in the Toxicity section.

10. In patients who had been treated with oxaliplatin, how much oxaliplatin were they subsequently able to receive?

Twelve patients were treated by bevacizumab plus FOLFOX. Among them, 10 had received oxaliplatin in a previous line.

11. The subgroup comparisons should be done with confidence intervals and not p-values.

This was done, with an update of the survival data.
Response to the reviewers

Manuscript MS:  1172410992367884
Title: Bevacizumab plus FOLFIRI or FOLFOX as third and further line treatment in metastatic colorectal cancer patients: a retrospective study.

Reviewer 2

- Minor essential revisions
  We corrected all the spelling mistakes detected by the reviewer

- Discretionary revisions
  - It may be interesting to specify the exclusion criteria in the eligibility criteria section for this retrospective study to complete the information provided regarding the sample selection.
    As suggested by the reviewer, we added in the Methods - Patients characteristics section the exclusion criteria: « The usual exclusion criteria were a history of major surgery within 28 days, a thrombotic or bleeding event within 6 months, a hypertension, a clinically significant cardiovascular disease, a hypertension, a therapeutic anti coagulation and the presence of brain metastases.

  - It would be valuable to provide some data about the non-bevacizumab related toxicities that were found in these patients. Once the 3rd and beyond treatment lines in metastatic colorectal cancer progressive to the more active chemotherapy regimens have to be carefully balanced with the adverse events associated profile and are faced to best supportive care in the clinical practice, the reader would benefit from a better knowledge of the tolerance to the chemotherapy re-challenge combined with the antibody.
    We added chemotherapy-induced toxicity, which are summarized in a additional table (Table 3) in the Toxicity section.

  - Regarding the survival analysis, it might be interesting to discuss the implications of the opened confidence intervals that are presented in the PFS and OS stratified analysis by treatment response.
    We have updated the survival data and specify all new confidence intervals in the Survival section.

  - In the discussion section, underlying the real subset of patients that could gain potential benefit from this treatment strategy and identifying the actual relevance of the group in the clinical practice would help to give an idea of the real weight of these findings in the clinical setting.
    Since bevacizumab is now indicated in combination with fluoropyrimidine-based chemotherapy in first or second line treatment of metastatic colorectal cancer, a small proportion of chemo-refractory patients will receive this anti-VEGF antibody, which limits the impact of our results in this clinical setting. However, the patients with a good performance status who did not previously receive bevacizumab, this therapeutic option remains as it was stated in the conclusion section of the manuscript.
Response to the reviewers

Manuscript MS: 1172410992367884
Title: Bevacizumab plus FOLFIRI or FOLFOX as third and further line treatment in metastatic colorectal cancer patients: a retrospective study.

Reviewer 3

This is an observational, retrospective study without control group, thus the level of evidence is very low and the authors have to remove the term "efficacy" from the manuscript. You cannot prove efficacy with this study design. The methods of testing (Fisher's Exact test, Kaplan Meier) and the definitions of OS and PFS are correct. The authors should use the Landmark method for their analysis of survival by response. The conclusion - need for a randomized trial - is sound.

As it was suggested by the reviewer, the term « Efficacy » was replaced by « activity ».

We do not understand what the reviewer wants with the Landmark method but we are at his disposal to change our statistical method after explanations.

The need for a randomized trial was added in the Conclusions section : « these results from retrospective data warrant prospective and randomized studies... »